## INTRODUCTION

Esophageal cancer is the sixth leading cause of cancer death worldwide. Japan is recognized as one of the high-risk areas, with an incidence in men of 10.0/100,000 compared with 5.8–6.2 of 100,000 in North America and Europe (1). Although the incidence rate varies geographically (1), a similar age distribution has been noted in Japan, Europe, and the United States, peaking at 70–79 years old. Populations aged ≥80 years have an almost identical incidence rate, which does not increase further (2–4). Therefore, in an aging society, the number of elderly patients presenting with this disease is expected to increase. Recent advances in therapy for esophageal cancer in younger patients, consisting of concomitant chemotherapy and radiotherapy (RT), transthoracic esophagectomy with thorough lymph node dissection, and combined chemoradiotherapy with surgery, are invariably associated with significant adverse events. In the elderly, these adverse events might offset the theoretical advantages (5–8). However, meticulous quality control in a therapeutic setting and appropriate patient selection are prerequisites for treatment decisions in the very elderly and need not exclude new approaches established in younger patients (9–13).

Chronologic age alone should therefore not be considered a determinant of treatment options. Although the importance of including the elderly in clinical trials has been emphasized (9, 14), the default clinical position currently remains conservative, with less-intensive interventions considered preferable for elderly patients (15, 18). Our retrospective survey revealed that, in patients aged ≥80 years, >80% were able to withstand single-modality high-dose RT without chemotherapy at a median total administered dose of 66 Gy within 6.5 weeks (17, 18). The planning target volume (PTV) was confined to the gross tumor volume in >80% of patients (18). In circumstances in which the treating physician considers that the patient is too old to tolerate concomitant chemotherapy, high-dose RT alone could represent a widely applicable approach in patients aged ≥80 years. On the basis of the data analyzed in these retrospective studies, we believe that it is essential to conduct a prospective evaluation of this approach in the very elderly to provide more extensive data on which to consider a strategy to cope with the controversies regarding adequate therapy and RT techniques in this age group.

## METHODS AND MATERIALS

### *Patient population*

The eligibility criteria for the study were patients ≥80 years of age with previously untreated, biopsy-proven squamous cell carcinoma located at the thoracic esophagus. In addition, the following eligibility criteria were used: no regional lymph adenopathy ≥1 cm in maximal diameter on computed tomography (CT) images (clinically N0); no evidence of distant organ metastasis (clinically M0); no radiologic findings of tumor invasion to the adjacent organs (clinically T1–T3, TNM classification, International Union Against Cancer, 1987); Zubrod performance status (PS) of 0–2; white blood cell count ≥3000/mm$^3$; hemoglobin level ≥7.5 g/dL; platelet count ≥50,000/mm$^3$; no history of other malignancies within 5 years before enrollment; no history of cardiac infarction, anginal attack, or symptomatic cerebrovascular accident during the 3 months immediately before enrollment; and no history of symptomatic cardiac or pulmonary insufficiency. All patients provided written informed consent. Patients who had intraepithelial tumor amenable to endoscopic mucosal resection were excluded. The local institutional ethics committees of all participating institutions approved this study.

### *Pretreatment evaluation*

The disease stage was determined from the results of physical examination, chest X-ray, barium swallow, esophageal endoscopy with biopsy, CT of the chest, and CT or ultrasonography of the neck and upper abdomen. A slice thickness of 5 mm was recommended for CT. The use of endoscopic ultrasonography was optional; therefore, the depth of tumor invasion was determined empirically (19). Bone scanning was done as indicated. Laboratory studies included a complete blood cell count, routine liver and kidney function tests, and electrocardiography. Information regarding preexisting comorbidities was collected at enrollment.

### *Treatment*

External beam RT to a dose of 66 Gy within 6.5 weeks using once-daily 2-Gy fractions was administered. The clinical target volume (CTV) was defined as the gross tumor volume with ≥3 cm of longitudinal margin. The lateral margin was left to the discretion of the treating physician because of the intrinsic vulnerability of cardiopulmonary function to thoracic RT in the elderly. The PTV was defined as the CTV plus an adequate margin to allow for physiologic organ motion and setup error. Prophylactic nodal RT covering the entire regional lymph node area was strictly prohibited when the whole CTV could be encompassed with a smaller PTV. RT was delivered using anterior-posterior (AP) opposed, followed by oblique (OBL) opposed beam arrangements. The total dose to the spinal cord was restricted to a maximum of 46 Gy. Treatment planning was done using CT-based or two-dimensional fluoroscopy simulations, depending on the resources available at the participating institution. The dose was prescribed to the center of the PTV, or the center of the beam axis for patients who underwent fluoroscopy simulation. Lung inhomogeneity corrections were not required. No other treatment was allowed, unless recurrence developed.

### *Outcome measures*

The primary endpoint of this study was the complete response (CR) rate. Evaluation of the response was done at 4 weeks after RT and consisted of physical and radiographic examinations identical to those conducted at the pretreatment evaluation. A CR was defined as maintained absence of tumor until the follow-up examination performed >4 weeks after the first evaluation. Patients were considered to have a non-CR when recurrence was observed at any site at this time. This trial used a two-stage design (20) in which 31 patients were to be enrolled initially. If <7 of these 31 patients achieved a CR, or ≥3 of the first 10 patients died of treatment-related complications, the trial would be stopped. Otherwise, enrollment would be extended to 53 patients and CR rate determined. Radiologic and endoscopic examinations were recommended at least once every 6 months thereafter. Overall and recurrence-free survival rates from the start of RT were measured using the Kaplan-Meier method; death from any cause was defined

as an event in calculating overall survival, and recurrence at any site or patient death was defined as an event in recurrence-free survival. Factors involved in univariate analyses were age, gender, PS, pretreatment hemoglobin level, presence or absence of comorbidity, T-classification, tumor length, and treatment-related variables (width, length, and margins for AP and OBL opposed portals, methods for treatment planning, and beam energy). Each factor was dichotomized; smaller than vs. equal to or larger than the median value, excluding gender, PS (0 vs. 1/2), T-classification (T1 vs. T2/3), methods for treatment planning (CT-based or fluoroscopy simulation for AP portals), and beam energy (6 MV or lower vs. 10 MV or higher). Statistical significance was evaluated with the log-rank test. Multivariate analyses were performed with Cox's proportional hazards model. All $p$ values were two-tailed. Assessment of toxicities was based on the National Cancer Institute Common Toxicity Criteria (version 2.0) and the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer Late Radiation Morbidity Scoring Scheme.

*Dose modifications*

Any toxicity of Grade 3 or worse, or pneumonitis/pulmonary infiltrates of Grade 2 or worse, required a treatment break. RT was resumed only when these toxicity grades were no longer present within 2 weeks of interruption.

*Quality review*

Case reports regarding schematic drawings of the tumor location and shape and size of the RT portals were required at enrollment. Diagnostic imaging, pathology reports, RT simulation and port films, and RT records were retrospectively reviewed by the principal investigator (M.K.) at the interim analysis and when this study was closed.

## RESULTS

*Patients*

Between January 1999 and April 2002, 53 patients were enrolled from 23 of the 41 institutions that had approved this protocol. One patient was excluded because of pleural effusion without cytologic examination, and one because of bedsores requiring daily care (PS 3). The characteristics of the 51 included patients from 22 institutions are listed in Table 1. Twenty-seven (53%) were reported as having at least one comorbidity, and 11 (20%) had two or more. The pretreatment chest X-rays were reviewed by the principal investigator for 49 patients, and a bilateral emphysematous change that was characterized by a flat and low hemidiaphragm (hyperinflated lung) associated with pulmonary vascular distortion (21) was observed in 21 (43%).

*Quality review*

Of the 22 institutions that enrolled evaluable patients, 11 (50%) used CT-based treatment planning for a total of 29 patients. However, 5 centers with a total of 11 patients used CT-based planning only for setting the OBL opposed portals and used fluoroscopy simulations for the AP opposed portals. The remaining 11 facilities used fluoroscopy simulation only for both AP opposed and OBL opposed portals. The maximal width of the AP opposed and OBL opposed portals was 5.0–9.0 cm (median, 7.0) and 4.0–9.0 cm (median, 6.2), respectively. An OBL opposed portal was not set for 1 patient because of

Table 1. Characteristics of 51 evaluable patients

| Characteristic | Patients |
|---|---|
| Age (y) | |
| Median | 83 |
| Range | 80–91 |
| ≤84 | 34 (67) |
| ≥85 | 17 (33) |
| Gender | |
| Female | 16 (31) |
| Male | 35 (69) |
| Zubrod performance status | |
| 0 | 21 (41) |
| 1 | 25 (49) |
| 2 | 5 (10) |
| Pretreatment hemoglobin level (g/dL) | |
| Median | 12.5 |
| Range | 8.6–15.4 |
| Clinical stage (UICC 1987) | |
| Stage I, T1N0 | 18 (35) |
| Stage IIA, T2N0 | 6 (12) |
| T3N0 | 27 (53) |
| Tumor length (cm) | |
| Median | 5 |
| Range | 2–11 |
| Tumor location* | |
| Upper | 2 (4) |
| Middle | 32 (63) |
| Lower | 17 (33) |
| Comorbidities | |
| None | 24 (47) |
| Single | 16 (31) |
| Multiple | 11 (22) |
| Cardiovascular | 19 (37) |
| Asymptomatic ECG abnormality | 8 (16) |
| Hypertension | 7 (14) |
| Arrhythmia requiring pacemaker | 1 (2) |
| Abdominal aortic aneurysm | 1 (2) |
| NOS | 3 (6) |
| Pulmonary | 3 (6) |
| Asymptomatic pleural adhesion | 2 (4) |
| NOS | 1 (2) |
| Emphysematous change on chest X-ray | 21 (43)† |
| Positive hepatitis C viral markers without clinical manifestations | 3 (6) |
| History of hemorrhagic gastric ulcer | 2 (4) |
| Rheumatoid arthritis requiring treatment | 2 (4) |
| Diabetes requiring insulin | 1 (2) |
| Hypothyloidism | 1 (2) |
| Hyperlipidemia requiring treatment | 1 (2) |

*Abbreviations:* UICC = International Union Against Cancers; ECG = electrocardiogram; NOS = not otherwise specified.

Data presented as number of patients, with percentages in parentheses, unless noted otherwise.

* Location of epicenter of tumor described according to following divisions: upper, from thoracic inlet to tracheal bifurcation; middle and lower, upper and lower half, respectively, of esophagus from tracheal bifurcation to esophagogastric junction.

† Of 49 patients whose chest X-rays were sent to principal investigator for central review.

Table 2. Results of radiotherapy quality review according to type of treatment planning and category of institutions

| | CT-based planning | | | | Fluoroscopy Simulation | | | | Total (%) |
|---|---|---|---|---|---|---|---|---|---|
| | N/R CC | Univ | Others | Total | N/R CC | Univ | Others | Total | |
| AP portals (n) | 10 | 6 | 2 | 18 | 12 | 12 | 9 | 33 | 51 (100) |
| Maximal tumor diameter on CT image (cm)* | | | | | | | | | |
| Median | 3.0 | 2.0 | | | 2.0 | 3.0 | 3.0 | | |
| Range | 2.0–3.5 | 2.0–5.0 | 2.0–4.5 | | 2.0–4.7 | 2.0–4.5 | 2.0–4.5 | | |
| Tumor Length (cm)* | | | | | | | | | |
| Median | 4.0 | 5.0 | | | 4.5 | 4.5 | 5.0 | | |
| Range | 3.0–9.0 | 4.0–10.0 | 4.0–8.0 | | 2.0–8.5 | 2.0–6.0 | 4.5–11.0 | | |
| Width (cm) | | | | | | | | | |
| <6.0 | | | | | 1 | | 2 | 3 | 3 (6) |
| 6.0–6.9 | 4 | 3 | 1 | 8 | 3 | 7 | 2 | 12 | 20 (41) |
| 7.0–8.0 | 4 | 3 | 1 | 8 | 8 | 5 | 3 | 16 | 24 (45) |
| >8.0 | 2 | | | 2 | | | 2 | 2 | 4 (8) |
| Lateral margin (cm) | | | | | | | | | |
| ≤1.0 | | | | | | 1 | 1 | 2 | 2 (4) |
| 1.1–2.0 | 4 | 4 | 2 | 10 | 7 | 10 | 5 | 22 | 32 (63) |
| 2.1–3.0 | 6 | 2 | | 8 | 5 | 1 | 2 | 8 | 16 (31) |
| >3.0 | | | | | | | 1 | 1 | 1 (2) |
| Length (cm) | | | | | | | | | |
| <14.0 | 3 | 2 | 1 | 6 | 6 | 10 | 3 | 19 | 25 (49) |
| ≥14.0 | 7 | 4 | 1 | 12 | 6 | 2 | 6 | 14 | 26 (51) |
| Longitudinal margin (cm) | | | | | | | | | |
| <3.0 | | | | | 1 | 1 | 2 | 4 | 4 (8) |
| 3.0–5.0 | 3 | 6 | 1 | 10 | 6 | 9 | 6 | 21 | 31 (61) |
| 5.1–7.0 | 4 | | 1 | 5 | 5 | 2 | 1 | 8 | 13 (25) |
| >7.0 | 3 | | | 3 | | | | | 3 (6) |
| OBL Portals† (n) | 12 | 14‡ | 2 | 28 | 9§ | 2§ | 9 | 20 | 48 (100) |
| Width (cm) | | | | | | | | | |
| <6.0 | 2 | 5 | 1 | 8 | 3 | 1 | 4 | 8 | 16 (33) |
| 6.0–6.9 | 5 | 9 | 1 | 15 | 5 | 1 | 4 | 10 | 25 (52) |
| 7.0–8.0 | 4 | | | 4 | 1 | | 1 | 2 | 6 (13) |
| >8.0 | 1 | | | 1 | | | | | 1 (2) |
| Length (cm) | | | | | | | | | |
| <14.0 | 6 | 9 | 1 | 16 | 6 | 2 | 7 | 15 | 31 (65) |
| ≥14.0 | 6 | 5 | 1 | 12 | 3 | | 2 | 5 | 17 (35) |
| Longitudinal margin (cm) | | | | | | | | | |
| <3.0 | | | | | 1 | 1 | 2 | 4 | 4 (8) |
| 3.0–5.0 | 8 | 14 | 2 | 24 | 4 | 1 | 6 | 11 | 35 (73) |
| 5.1–7.0 | 2 | | | 2 | 4 | | 1 | 5 | 7 (15) |
| >7.0 | 2 | | | 2 | | | | | 2 (4) |

*Abbreviations:* N/R CC = national or regional cancer center; Univ = university; OBL = oblique.
* At time of treatment planning for AP opposed portals.
† Lateral margins regarding OBL opposed portals were not reviewed because assessment of radiotherapy-inducing tumor shrinkage was not possible with available material.
‡ One patient did not receive OBL opposed portal because of early death.
§ Materials for review were unavailable in 1 patient.

early death. The pretreatment CT, RT simulation films, and port films were reviewed in 49 patients (96%). The maximal tumor diameter on CT was 2.0–4.7 cm (median, 2.8). The lateral margin of the AP opposed portals [(maximal width of AP opposed portals − maximal tumor diameter)/2] was 0.8–3.3 cm (median, 2.0). The lateral margins in the context of the OBL opposed portals were not reviewed because assessment of RT-inducing gross tumor volume shrinkage was not possible with the available materials. The length of the AP opposed and OBL opposed portals was 10.0–22.6 cm (median, 13.6) and 7.0–18.6 cm (median, 12.0), respectively. The longitudinal margin [(field length − reported tumor length)/2] of the AP opposed and OBL opposed portals was 2.0–9.0 cm (median, 4.0) and 1.0–9.0 cm (median, 4.0), respectively. We divided the participating institutions into three categories (national/regional cancer center [$n$ = 6], universities [$n$ = 10], and other [$n$ = 6]) to assess whether the type of treating institution or treatment planning method influenced the treatment outcomes (Table 2). No

Table 3. Number of patients who experienced adverse events within 90 days from start of radiotherapy

| Event | Grade 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|
| Odynophagia | 16 | 7 | 2 | | |
| Pneumonitis/pulmonary infiltrates | | 1 | | | 2 |
| Pneumonia | | | | | 1 |
| Cardiac angina | | | 1 | | |
| General malaise | | | 1 | | |
| White blood cell | 11 | 5 | | | |
| Mediastinitis | | 1 | | | |
| Maximal grade reported per patient | 18 | 10 | 4 | 0 | 3 |

statistically significant differences in maximal width or lateral or longitudinal margins were found among the three types of institutions or treatment planning methods ($p > 0.200$, Mann-Whitney $U$ test). Four patients (8%) had AP opposed and OBL opposed portals set at a <3-cm longitudinal margin. Thirteen patients (25%) had AP opposed and/or OBL opposed portals with a >5.0-cm longitudinal margin owing to discretionary decisions of the responsible physicians. Another 3 patients (6%) had AP opposed and/or OBL opposed portals with a >7.0-cm longitudinal margin; 2 with Stage T1 disease associated with multiple superficial lesions included in the CTV by the responsible physician and 1 with Stage T1 disease in the middle thoracic esophagus who received prophylactic nodal RT to the right recurrent nerve lymph node (0.5-cm maximal diameter). All but 1 patient received intentional prophylactic nodal RT. The total administered radiation dose with AP opposed portals was 40–44 Gy (median, 40 Gy). Neither the width (<7 vs. ≥7 cm) nor the length (<14 vs. ≥14 cm) of the AP opposed portals correlated significantly with the T stage (T1 vs. T2–T3) or tumor length (<5 vs. ≥5 cm) using the chi-square test ($p > 0.100$). All patients received RT using a linear accelerator; 4, 12, 32, 1, and 3 patients received RT using 4-, 6-, 10-, 15-, and 20-MV X-rays, respectively.

*Acute adverse events*

Radiotherapy was completed as planned in 47 patients (92%), with an elapsed treatment time of 43–58 days (median, 49 days). A total of 7 patients (14%) experienced Grade 3 or worse acute adverse events (Table 3). Three patients died of treatment-related causes—two died suddenly of acute respiratory distress syndrome 7 days after RT completion, and one, whose treatment was discontinued at 34 Gy because of bacterial pneumonia, died as a consequence 7 days later. Two other patients could not complete RT because of acute Grade 3 adverse events (cardiac angina at 64 Gy in one and treatment refusal owing to fatigue at 56 Gy in the other). One patient, who had stopped RT because of anginal attacks, had a history of angina pectoris before enrollment; no other attack was observed after RT until her death from persistent local disease at 6.6 months. Two patients with Stage T3 disease experienced transient Grade 3 odynophagia during RT or immediately after RT completion. However, both patients survived for >4 years without symptomatic esophageal stenoses. Another 10 patients (20%) experienced Grade 2 acute adverse events. One patient discontinued RT because of persistent Grade 2 pneumonitis/pulmonary infiltrates at 48 Gy. One patient with T3 disease experienced mediastinitis at 36 Gy requiring a 2-day treatment break was able to complete RT within 53 days without any further complications until his death from local failure at 18 months. Otherwise, this protocol was well

Table 4. Patterns of failure

| | T1 ($n$ = 18) | | T2–T3 ($n$ = 33) | | |
|---|---|---|---|---|---|
| | CR | Non-CR | CR | Non-CR | Total (%) |
| Patients ($n$) | 15 | 3 | 16 | 17 | 51 (100) |
| Site of first failure | | | | | |
| Local | 5 | | 3 | 15 | 23 (45) |
| Nodal | 2 | | 3 | 1 | 6 (12) |
| Distant | 1 | 1 | 2 | | 4 (8) |
| No failure* | 7 | 2 | 8 | 1 | 18 (35) |
| Survival outcome* | | | | | |
| Alive without disease | 6 | 2 | 4 | 1 | 13 (25) |
| Alive with disease | | 1 | | | 1 (2) |
| Died of index cancer | 7 | | 9 | 15 | 31 (61) |
| Died of other causes | | | | | |
| Lung cancer | 1† | | | | 1† (2) |
| Gastric cancer | | | 2 | | 2 (4) |
| Pancreas cancer | 1 | | | | 1 (2) |
| Vascular accidents | | | 1 | 1 | 2 (4) |

*Abbreviation:* CR = complete response.
* At time of this analysis, when all surviving patients had been followed for >2 y.
† Died of lung cancer after successful salvage for local recurrence of esophageal cancer.

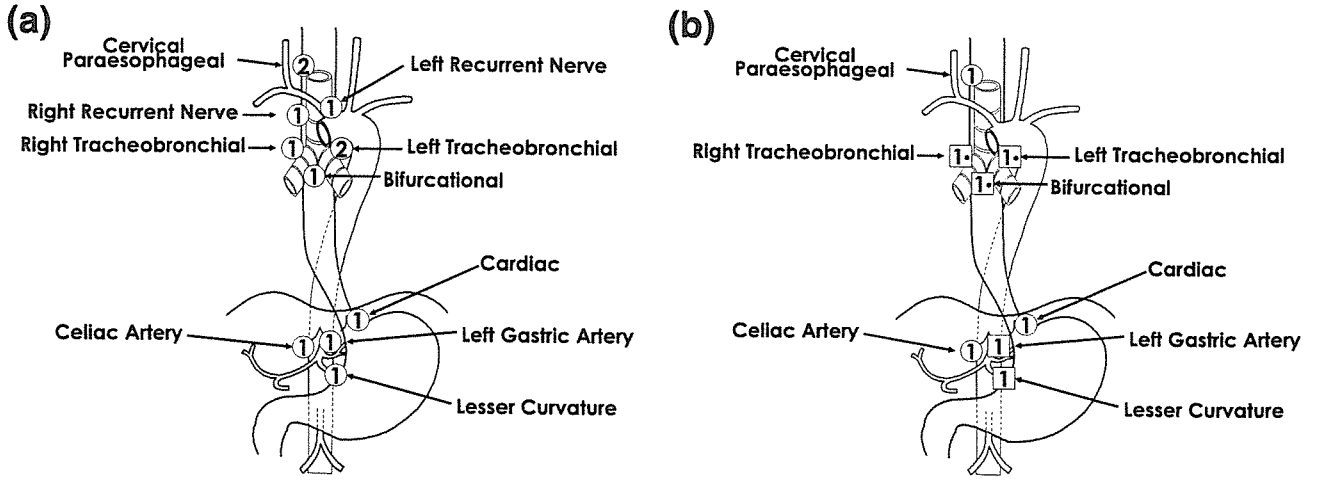


Fig. 1. Incidence of regional lymph node failure in relation to nodal site expressed as (a) cumulative overall or (b) first site of failure. Numbers with same symbol (asterisks) show recurrences occurring in same patients simultaneously. Squares indicate patients who experienced simultaneous distant organ metastasis.

tolerated, and all hematologic toxicities were temporary, not necessitating interruption of RT.

*Failure patterns*

Thirty-one of 51 evaluable patients (61%) were reported as experiencing a CR, which was confirmed using endoscopy in 15, barium swallow in 3, and both in 13. Confirmatory biopsy was done in 3 patients. The CR rates for each T stage were as follows: 83% (15 of 18), T1; 50% (3 of 6), T2; and 48% (13 of 27), T3. The patterns of treatment failure are listed in Table 4. A total of 23 patients had local failure at 0–48 months, and 21 (91%) within 2 years. Of the 20 non-CR patients, 5 (Stage T1 in 3, T2 in 1, and T3 in 1) had not experienced local progression for 27–60 months. No newly developed esophageal cancer occurred outside the PTV. The actuarial rate for control of the primary tumor at 3 years for patients with Stage T1 and T2–T3 disease was 70% (95% confidence interval [CI], 48–92%) and 21% (95% CI, 7–35%), respectively. A total of 8 patients experienced nodal failure. In 6 of them, this occurred as their first event at 7–43 months (median, 25 months) and was associated with simultaneous distant metastasis in 3. All 8 nodal recurrences occurred outside the PTV. The distribution of nodal failure in relation to the anatomic sites is illustrated in Fig. 1. A total of 12 patients experienced distant failure, 8 of whom had had previous local or nodal failure. Distant failure was observed in the lungs in 9, liver in 1, and abdominal para-aortic lymph node below the celiac axis in 2.

*Salvage treatment*

Two patients who originally had Stage T1 and T2 disease underwent surgery for local failure at 9 and 6 months. The patient with Stage T1 disease experienced nodal failure at 18 months and died at 52 months of nodal and distant failure despite additional RT for nodal recurrence. The patient with Stage T2 disease was alive and disease free at 36 months. Two patients with T1 disease underwent successful salvage endoscopic mucosal resection at 16 and 48 months; however, one died of acute respiratory distress syndrome at 36 months and one of lung cancer at 59 months. Two patients received RT for nodal recurrence, and one received cisplatin and 5-fluorouracil for pleural dissemination. They subsequently died within 12 months.

*De novo malignancies*

Nine newly developed malignancies (three gastric cancers, three lung cancers, one cancer of the ureter, one pancreas cancer, and one skin cancer in the head-and-neck region) were observed in 8 patients at 4–42 months (median, 26 months). Four were fatal (Table 4). One patient died of preexisting nodal failure of the esophageal cancer at 49 months, and one died of cerebral hemorrhage with lung cancer at 58 months. Two patients were successfully treated and were alive without disease at 31 and 60 months.

*Survival outcomes*

All but 1 patient could be followed for >2 years or until death. One patient with persistent disease was lost to follow-up at 7 months and was considered to have died of the

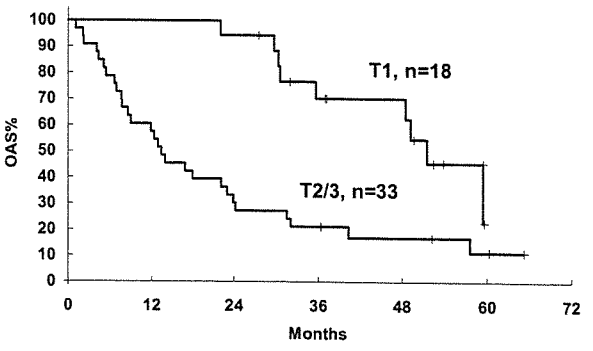


Fig. 2. Overall survival in relation to T stage.

index cancer at that time. The median follow-up period for surviving patients was 47 months (range, 27–65 months). At the present analysis in June 2005, 37 patients had died. The details of the causes of death are shown in Table 4. The median survival time was 30 months, and the 1-, 2-, and 3-year overall survival (OS) rate was 71% (95% CI, 58–83%), 53% (95% CI, 39–67%), and 39% (95% CI, 24–52%), respectively. Univariate analysis revealed that T stage and PS were the only factors that correlated significantly with OS. The median survival time and OS rate at 3 years was 51 months and 70% (95% CI, 48–92%) for T1 and 14 months and 21% (95% CI, 7–35%) for T2–T3 disease, respectively ($p < 0.001$, Fig. 2). No statistically significant differences were found in OS rate between patients with Stage T2 and T3 disease ($p = 0.416$). Patients with PS 0 achieved an OS rate of 61% at 3 years (95% CI, 39–82%); however, patients with PS 1 or 2 had an OS rate of 23% (95% CI, 8–38%; $p = 0.034$). Tumor length had marginal significance, with a 3-year OS rate of 45% (95% CI, 24–65%) vs. 32% (95% CI, 15–51%) for those with tumors <5 cm vs. ≥5 cm, respectively ($p = 0.080$). Multivariate analysis involving T stage, PS, and tumor length revealed that T stage was the only independent prognostic factor, with a hazard ratio of 3.1 (95% CI, 1.3–7.3, $p = 0.012$). The recurrence-free survival rate at 3 years for patients with Stage T1 and T2–T3 disease was 52% (95% CI, 28–77%) and 12% (95% CI, 1–23%), respectively ($p = 0.002$).

*Late adverse events*

Apart from the three treatment-related deaths, six late cardiopulmonary adverse events of Grade 3 or worse were observed (Table 5). None of these 6 patients experienced cardiopulmonary adverse events during the acute phase. Symptomatic pericardial effusion was observed in 4 patients; 1 died with superficial local recurrence at 30 months, 2 required drainage, and 1 presented with mild dyspnea that resolved spontaneously. One patient died at 36 months of acute respiratory distress syndrome after drainage of a massive pleural effusion with negative cytologic findings. The actuarial incidence of these late cardiopulmonary complications was 17% (95% CI, 5–29%) and 26% (95% CI, 10–42%) at 2 and 3 years, respectively, when the 3 patients who died of treatment-related causes were included. The factors influencing the incidence of these serious cardiopulmonary toxicities were analyzed regarding the presence of either emphysematous changes or cardiovascular comorbidity, in addition to the factors involved in OS. Univariate analysis revealed that the width ($p = 0.013$) and length ($p = 0.016$) of the AP opposed portals correlated significantly with the incidence (Fig. 3), but the others were not ($p > 0.200$). One patient required repetitive blood transfusions for hemorrhagic esophageal erosion for >4 years, despite dietary vigilance. Two patients developed cognitive dysfunctions and subsequently died, 1 at 6 months without evidence of recurrence and 1 at 12 months after local recurrence. No esophageal stricture requiring repetitive dilation was reported in the patients who survived and were recurrence free.

## DISCUSSION

This study explored the validity of the RT procedures widely applied to elderly patients in Japan. Our results have demonstrated that RT can be completed in 92% of patients. Also, the median survival time for all patients was 30 months, with a 3-year OS rate of 39%. The actuarial inci-

Table 5. Moderate or severe cardiopulmonary/esophageal adverse events

| Age (y), Gender, Tumor location, length | T stage | Events | Maximal Width/length of AP Portal (cm) | Onset of events (mo) | Clinical course | Final grade* | Outcome (mo) |
|---|---|---|---|---|---|---|---|
| 87, M, middle, 10 cm | 3 | Pneumonitis | 8.5 × 15.0 | 2 | Fatal | 5 | 2, TRD |
| 80, M, middle, 6 cm | 3 | Pneumonitis | 7.0 × 16.0 | 2 | Fatal | 5 | 2, TRD |
| 80, M, lower, 6 cm | 2 | Pneumonia | 7.0 × 12.0 | 1 | Fatal | 5 | 1, TRD |
| 81, M, middle, 4 cm | 1 | Pleural effusion | 7.9 × 21.0† | 5 | Fatal ARDS after drainage | 5 | 36, DID |
| 82, M, middle, 4 cm | 1 | Pericardial effusion | 7.2 × 19.0 | 17 | Fatal cardiac insufficiency | 5 | 30, DID |
| 80, F, lower, 4 cm | 1 | Pericardial effusion | 7.0 × 14.0 | 25 | Drainage | 4 | 52, NED |
| 80, M, middle, 3 cm | 3 | Pericardial effusion | 7.0 × 14.0 | 13 | Drainage | 4 | 32, DOD |
| 80, F, middle, 6 cm | 3 | Arrhythmia (arterial flatter) | 7.0 × 14.0 | 19 | Resolved with medication | 3 | 60, NED |
| 84, M, middle, 8 cm | 1 | Pericardial effusion | 6.0 × 14.0 | 12 | Resolved without drainage | 3 | 48, DOD |
| 85, F, lower, 3 cm | 3 | Esophageal erosion | 7.6 × 16.0 | 12 | Requiring repetitive BTF | 3 | 52, NED |

*Abbreviations:* M = male; F = female; ARDS = adult respiratory distress syndrome; TRD = treatment-related death; NED = alive without disease; DID = died of causes other than index cancer; DOD = died of index cancer; BTF = blood transfusion; mo = months; AP = antero-posterior.

* According to Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer Late Radiation Morbidity Scoring Scheme; esophageal erosion scored as Grade 3 because disabling anemia was not experienced.

† Prophylactic nodal irradiation encompassing right recurrent nerve lymph nodes was done.

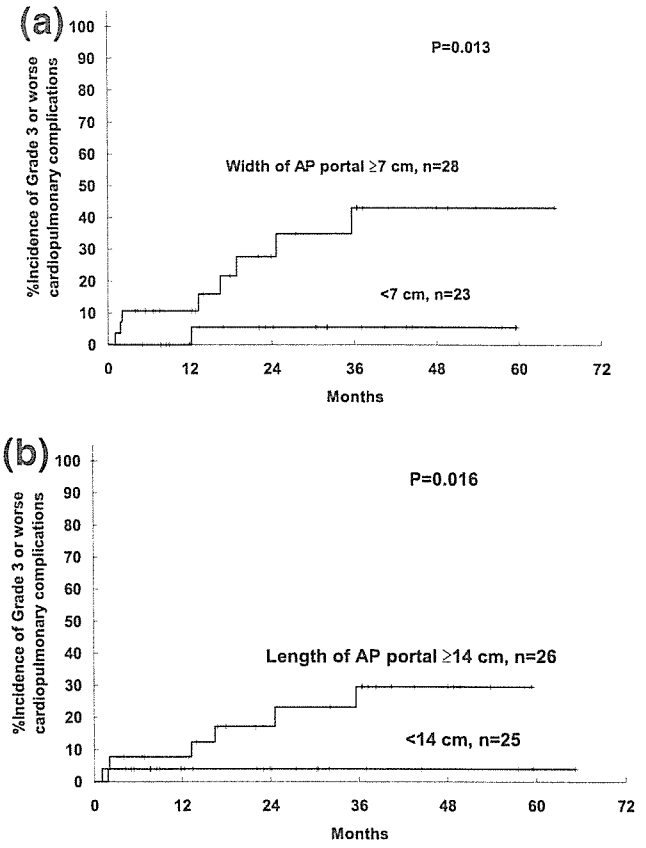


Fig. 3. Actuarial incidence of Grade 3 or worse cardiopulmonary complications in relation to (a) maximal width and (b) length of antero-posterior (AP) opposed portals.

dence of Grade 3 or worse cardiopulmonary adverse events was 26% at 3 years, and a significant correlation with the size of the AP opposed portal was suggested. Finally, although all nodal recurrences as a first event occurred outside the PTV in 6 patients, 3 had simultaneous distant metastasis.

Retrospective studies have shown that 70–89% of patients aged 75 to ≥80 years can be treated with a total dose of ≥60 Gy (16, 17). That 92% of our patients completed RT at 66 Gy in 33 fractions suggests that their physical sturdiness was somewhat greater than the average seen in daily clinical practice, despite the relaxation of the eligibility criteria. Although the survival outcomes for all patients were reasonable, this was because of patient selection (i.e., 35% of patients had Stage I disease). The heterogeneity of the physical and psychosocial backgrounds was greater in the elderly compared with younger patients (14). Therefore, a positive selection bias might be an important confounding factor when applying the results of clinical trials of elderly patients to daily clinical practice. In other words, many patients aged ≥80 years may well be able to tolerate radical RT, provided they are preselected for medical fitness. However, for patients with advanced disease (Stage T2–T3, $n$ = 33), the outcomes in this study were unsatisfactory, as expected.

Regarding OS after single-modality high-dose RT in younger patients, Earlam and Cunha-Melo (22) reported that the considerable variation in the OS rate at 2 years (range, 8–27%), mainly resulted from patient selection. More recent series have also shown OS rates of 0–27% and 21% at 3 and 5 years, respectively, after RT, with or without neoadjuvant chemotherapy (5, 23–25). Considering the heterogeneity of patient selection, as well as the differences in the length of follow-up in these studies, a 21% OS rate at 3 years for patients with T2–T3 disease in our study actually seems comparable to that reported in younger patients receiving RT alone.

Although a 4% incidence of fatal radiation-induced pneumonitis, and the overall 6% occurrence of early death, in this prospective study drew attention to safety issues when applying this regimen of high-dose RT for the elderly, what was even more important was the 26% actuarial incidence of Grade 3 or worse cardiopulmonary complications at 3 years. A quality review was done retrospectively because we did not have sufficient resources for an initial review, and, more importantly, the RT technique tested in this study was already widely applied in Japan. Because of this, very heterogeneous definitions of CTV and PTV were current among the large number of participating institutions. This represents a major problem for this study. In addition, the RT technique used was already considered outdated at most RT facilities in the United States, where three-dimensional RT planning with CT is routinely performed (26). The crude incidence rate of severe or life-threatening cardiopulmonary complications after RT alone at the acute and late phases has been reported as between 0% and 18% using multiple field techniques (27, 28) or brachytherapy (29). Other investigators have reported a 0–9% crude incidence rate of acute and late cardiopulmonary toxicity (16, 23, 30), although details on severity were not provided. Among the different patient- and treatment-related factors analyzed, only the width and length of the AP opposed portals correlated significantly with the incidence of cardiopulmonary complications. This multicenter study could not provide dose–volume histogram analysis regarding acute and late toxicity (31), because facilities that had limited resources for performing three-dimensional RT planning were involved. Nevertheless, all the late cardiopulmonary complications of Grade 3 or worse occurred in patients whose tumors were located in the middle and lower third of the esophagus. This implies that the size of the AP opposed portals relates directly to the volume of heart irradiated, which has a threshold radiation dose in conventional fractionation of approximately 35–40 Gy before developing clinically manifested signs and symptoms over long periods in younger patients (32). Independent of the RT technique and quality control used in this study, changes in inflammatory response, as well as insidious comorbidities in the very elderly, may also have contributed to the unexpectedly high overall incidence of adverse cardiopulmonary events (11). Therefore, reducing the margins from the generally applied 2 cm in the lateral and 5 cm in the longitudinal direction for defining the CTV (33–35), especially in the elderly, may have critical importance, particularly because

the median diameter and length of the primary tumors in our study was 2.8 cm and 5 cm, respectively, even in preselected patients.

In addition to using a multiple-field technique, brachytherapy (29) and particle beam therapy (36) are theoretically better ways to administer high-dose RT more safely. However, dose escalation, with or without concomitant chemotherapy, failed to show survival benefits compared with modest-dose RT (50.4 Gy in 5.5 weeks) concomitant with chemotherapy in randomized studies (5, 33). On the basis of currently available data, the best way to reduce the high-dose volume of the heart is to reduce the total radiation dose. Studies testing the applicability of established nonsurgical approaches in older patients are awaited. Single-modality approaches using alternative RT techniques as described above should mainly focus on medically unfit older patients who were appropriately judged as intolerant of cytotoxic treatments (14). Most importantly, all clinical trials testing RT should be performed with an investment in meticulous and long-term observation by the radiation oncologist responsible, and estimation of the incidence of adverse events with actuarial, not crude, statistics (37) to facilitate comparisons between modalities.

The incidence of nodal recurrence in patients with node-negative disease was high, as expected, from the nature of this disease (35) and the potential inaccuracy of CT-based tumor/node staging (19) in this study. This applied to 6 of our patients, one-half of whom also had distant failure. Therefore, at least 3 (6%) of 51 patients could have benefited from comprehensive elective nodal RT from the lower cervical nodes down to the celiac root with appropriate margins. Nodal involvement is associated with a marked decrease in survival compared with truly localized disease (13, 38), and intensive efforts to improve local control for advanced primary tumor have failed to deliver satisfactory results to date (7, 8, 23, 33). Adding to the risk of late cardiopulmonary complications, large portals increasing the irradiated volume of the normal lung might have a negative impact on possible salvage surgery (39), even though only 2 (10%) of 21 patients experiencing local failure not amenable to endoscopic mucosal resection benefited from this procedure in the present series. Therefore, a tradeoff of the benefits and risks of comprehensive nodal RT should be carefully evaluated further in patients aged >80 years with advanced disease.

## CONCLUSION

Localized external beam RT at 66 Gy within 6.5 weeks as a single-treatment modality for clinical Stage T1–3N0 squamous cell carcinoma of the thoracic esophagus in patients aged ≥80 years yielded results comparable to those reported in younger patients. A CTV with <2-cm radial and 5-cm longitudinal margins around the tumor seems more desirable in the elderly than in younger patients. Accordingly, close collaboration between the diagnostic and treating physicians for adequate target definition, as well as strict quality control of the RT procedure involving technologists and medical physics staff that maximizes the therapeutic ratio, are critical for reducing long-term cardiopulmonary toxicity. The benefits of elective nodal irradiation, especially for patients with poor local control expected, should be carefully considered. To optimize the therapy for this disease, long-term and careful monitoring and reporting of late adverse events to facilitate comparisons between modalities is essential, especially in the elderly. On these premises, well-designed trials testing concomitant chemotherapy with RT using more limited PTV are warranted for the elderly, who represent an increasing proportion of patients with this disease.

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ORIGINAL REPORT

# Phase II Study of Radiotherapy Employing Proton Beam for Hepatocellular Carcinoma

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## ABSTRACT

### Purpose
To evaluate the safety and efficacy of proton beam radiotherapy (PRT) for hepatocellular carcinoma.

### Patients and Methods
Eligibility criteria for this study were: solitary hepatocellular carcinoma (HCC); no indication for surgery or local ablation therapy; no ascites; age ≥ 20 years; Zubrod performance status of 0 to 2; no serious comorbidities other than liver cirrhosis; written informed consent. PRT was administered in doses of 76 cobalt gray equivalent in 20 fractions for 5 weeks. No patients received transarterial chemoembolization or local ablation in combination with PRT.

### Results
Thirty patients were enrolled between May 1999 and February 2003. There were 20 male and 10 female patients, with a median age of 70 years. Maximum tumor diameter ranged from 25 to 82 mm (median, 45 mm). All patients had liver cirrhosis, the degree of which was Child-Pugh class A in 20, and class B in 10 patients. Acute reactions of PRT were well tolerated, and PRT was completed as planned in all patients. Four patients died of hepatic insufficiency without tumor recurrence at 6 to 9 months. Three of these four patients had pretreatment indocyanine green retention rate at 15 minutes of more than 50%. After a median follow-up period of 31 months (16 to 54 months), only one patient experienced recurrence of the primary tumor, and 2-year actuarial local progression-free rate was 96% (95% CI, 88% to 100%). Actuarial overall survival rate at 2 years was 66% (48% to 84%).

### Conclusion
PRT showed excellent control of the primary tumor, with minimal acute toxicity. Further study is warranted to scrutinize adequate patient selection in order to maximize survival benefit of this promising modality.

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## INTRODUCTION

Cirrhosis is found in more than 80% of patients with hepatocellular carcinoma (HCC). This precludes more than 70% of the patients from receiving potentially curative treatments, and also contributes eventually to fatal hepatic insufficiency and multifocal tumorigenesis.[1,2] Approximately 50% to 70% and 30% to 50% of 5-year overall survival was achieved with surgery including liver transplantation[3-6] and percutaneous local ablation,[7-9] respectively, for an adequately selected population of patients. However, no standard strategy has been established for patients with unresectable HCC at present.

Partial liver irradiation for HCC using 50 to 70 Gy of megavoltage x-ray with or without transarterial chemoembolizaztion (TACE) for 5 to 7 weeks has been widely applied during the last two decades. This resulted in response rates of 33% to 67%, with a median survival period of 13 to 19

months and 10% to 25% overall survival at 3 years.[10-12] Since 1985, proton radiotherapy (PRT) administered at a median dose of 72 cobalt gray equivalent ($Gy_E$) in16 fractions during 3 weeks with or without TACE, had been applied in more than 160 patients with HCC at the University of Tsukuba, resulting in a more than 80% local progression-free survival rate with 45% and 25% overall survival at 3 and 5 years, respectively.[13,14] The excellent depth-dose profile of the proton beam enabled us to embark on an aggressive dose escalation while keeping a certain volume of the noncancerous portion of the liver free from receiving any dose of irradiation. This single-institutional, single-arm, prospective study was conducted to confirm encouraging retrospective results of PRT for HCC using our newly installed proton therapy equipment.

## PATIENTS AND METHODS

### Patient Population

Patients were required to have uni- or bidimensionally measurable solitary HCC of ≤ 10 cm in maximum diameter on computed tomography (CT) and/or magnetic resonance (MRI) imaging. In addition, the following eligibility criteria were required: no history of radiotherapy for the abdominal area; no previous treatment for HCC within 4 weeks of inclusion; no evidence of extrahepatic spread of HCC; age ≥ 20 years; Zubrod performance status (PS) of 0 to 2; WBC count ≥ 2,000/$mm^3$; hemoglobin level ≥ 7.5 g/dL; platelet count ≥ 25,000/$mm^3$; and adequate hepatic function (total bilirubin ≤ 3.0 mg/dL; AST and ALT < 5.0× upper limit of normal; no ascites). Patients who had multicentric HCCs were not considered as candidates for this study, except for those with the following two conditions: (1) multinodular aggregating HCC that could be encompassed by single clinical target volume; (2) lesions other than targeted tumor that were judged as controlled with prior surgery and/or local ablation therapy. Because a planned total dose would result in a significant likelihood of serious bowel complications, patients who had tumors abutting or invading the stomach or intestinal loop were excluded. The protocol was approved by our institutional ethics committee, and written informed consent was obtained from all patients.

### Pretreatment Evaluation

All patients underwent indocyanine green clearance test, and the retention rate at 15 minutes (ICG R15) was measured for the purpose of quantitative assessment of hepatic functional reserve. CBC, biochemical profile including total protein, albumin, total cholesterol, electrolytes, kidney and liver function tests, and serological testing for hepatitis B surface antigen and antihepatitis C antibody were done. C-reactive protein and tumor markers including alpha feto-protein and carcinoembryonic antigen were also measured. Chest x-ray was required to exclude lung metastasis. All patients were judged as unresectable by expert hepatobiliary surgeons in our institution, based on their serum bilirubin level, ICG R15, and expected volume of resected liver.[15] Gastrointestinal endoscopy was done to exclude active ulcer and/or inflammatory disease located at the stomach and the duodenum. All patients underwent abdominal ultrasonography, triphasic CT or MRI, CT during arteriography and arterial portography.[16] Diagnosis of HCC was based on radiographic findings on triphasic CT/MRI. Radiologic criteria for HCC definition were as follows: tumor showing high attenuation during hepatic arterial and portal venous phase indicating hypervascular tumor; tumor showing low attenuation during delayed phase indicating rapid wash-out of contrast media. Confirmatory percutaneous fine-needle biopsies were required for all patients unless they had radiologically compatible, postsurgical recurrent HCC. Tumors that broadly abut on the vena cava, portal vein, or hepatic vein that were associated with caliber changes and/or filling defects of these vessels, were tentatively defined as positive for macroscopic vascular invasion. One patient had visible tumor on fluoroscopy because of residual iodized oil contrast medium used in previous TACE. For the other 29 patients, one or two metallic markers (inactive Au grain of which the diameter and length were 1.1 mm and 3.0 mm, respectively) were inserted percutaneously at the periphery of the target tumor.

### Treatment Planning

PRT was performed with the Proton Therapy System (Sumitomo Heavy Industries Ltd, Tokyo, Japan), and treatment planning, with the PT-PLAN/NDOSE System (Sumitomo Heavy Industries Ltd). In this system, the proton beam was generated with Cyclotron C235 with an energy of 235 MV at the exit. Gross tumor volume (GTV) was defined using a treatment planning CT scan using X Vision Real CT scanner (Toshiba Co Ltd, Tokyo, Japan), and clinical target volume (CTV) and planning target volume (PTV) were defined as follows: CTV = GTV + 5 mm, and PTV = CTV + 3 mm of lateral, craniocaudal, and anteroposterior margins. Proton beam was delivered with two-beam arrangement to minimize irradiated volume of noncancerous liver using our rotating gantry system. The beam energy and spread-out Bragg peak[13] were fine-tuned so that 90% isodose volume of prescribed dose encompassed PTV. To evaluate the risk of radiation-inducing hepatic insufficiency, dose-volume histogram (DVH) was calculated for all patients.[17]

Scanning of CT images for both treatment planning and irradiation of proton beam were done during the exhalation phase using a Respiration-Gated Irradiation System (ReGIS). Our ReGIS during this study period was composed in the following manner: strain gauge, which converts tension of the abdominal wall into electrical respiratory signal, was put on the abdominal skin of the patient; gating signal triggering CT scanning or proton beam was generated during the exhalation phase.

### Treatment

The fractionation and dosage in this study were based on the results of a retrospective study at the University of Tsukuba. A total dose ranging from 50 $Gy_E$ in 10 fractions to 87.5 $Gy_E$ in 30 fractions (median, 72 $Gy_E$ in16 fractions) was administered without serious acute and late adverse events. All patients received PRT to a total dose of 76 $Gy_E$ for 5 weeks in 3.8-$Gy_E$ once-daily fractions, four fractions in a week using 150 to 190 MV proton beam. Relative biologic effectiveness of our proton beam was defined as 1.1. No concomitant treatment (eg, TACE, local ablation, systemic chemotherapy) was allowed during and after the PRT, unless a treatment failure was detected. Verification of patient set-up was done in each fraction using a digital radiography subtraction system. In this system, fluoroscopic images obtained at daily set-up were subtracted by the original image that was taken at the time of treatment planning. Position of the patient couch was adjusted to overlap the diaphragm, inserted metallic markers, and bone landmarks on the original position at the end of the exhalation phase.

PRT was administered 4 days a week, mainly Monday to Thursday, and Friday was reserved for maintenance of the PRT system. Predefined adverse reaction of PRT was dermatitis, pneumonitis, hepatic insufficiency, and gastrointestinal ulcer and/or bleeding. If one of these reactions of grade 3 or higher, or unexpected reactions of grade 4 or higher were observed in three patients, further accrual of patients was defined to be stopped. No further PRT was allowed when grade 4 hematologic toxicity or any of the toxicities of grade 3 or higher were observed at the digestive tract or lung. PRT was delayed up to 2 weeks until recovery when an acute nonhematologic toxicity of grade 3 or higher, other than that described above, was observed. However, when only an elevation of liver enzymes was observed without manifestation of clinically significant signs and symptoms, PRT was allowed to be continued according to the physician's judgment.

### Outcomes

It has been reported that the tumor, although achieving a complete response, persisted over a long period, ranging from 3 weeks to 12+ months after the completion of PRT.[18] Therefore, a local progression-free survival rate at 4 weeks after the end of PRT was adopted as the primary end point of this study, where an event was defined as progression of the primary tumor with size increase of more than 25%, in order to facilitate an interim analysis as described in the Statistical Design section below. Assessment of primary tumor response using CT and/or MRI was performed 4 weeks after the completion of PRT. Overall survival and disease-free survival rates were also evaluated as secondary end points. Death of any cause was defined as an event in calculation of overall survival, whereas tumor recurrences at any sites or patient deaths were defined as events for disease-free survival. Adverse events were reviewed weekly during the PRT by means of physical examination, CBC, liver function test, and the other biochemical profiles as indicated. The severity of adverse events was assessed using the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2.0. After completion of PRT, reviews monitoring disease status, including CT and/or MRI examinations and long-term toxicity were done at a minimum frequency of once every 3 months.

### Statistical Design

The null hypothesis of a true local progression-free rate of 50% or lower was based on average results of photon radiotherapy reported from Japan, in which each study accumulated approximately 20 patients.[11,12] This was tested against the alternative hypothesis of a true rate of 80% or higher with an $\alpha$ level of 5% and a power of 80%, which required 30 patients according to the method by Makuch and Simon.[19] If fewer than five patients experienced local progression-free status within 4 weeks postirradiation at the end of first nine enrollments, the trial would be stopped. Otherwise, if more than 24 patients remained locally progression-free among the total of 30 patients, this would be sufficient to reject the null hypothesis and conclude that PRT warrants further study. Time-to-event analyses were done using Kaplan-Meier estimates, and 95% CIs were calculated. The difference of time-to-event curve was evaluated with the log-rank test. Multivariate analyses were performed with Cox's proportional hazards model.

## RESULTS

### Patients

Thirty patients were enrolled between May 1999 and February 2003. Patient characteristics at the start of PRT are

**Table 1.** Characteristics of 30 Enrolled Patients

| Characteristic | Patients No. | Patients % |
|---|---|---|
| Age, years | | |
| Median | 70 | |
| Range | 48-87 | |
| Sex | | |
| Male | 20 | 67 |
| Female | 10 | 33 |
| ECOG performance status | | |
| 0-1 | 29 | 97 |
| 2 | 1 | 3 |
| Clinical stage (2) | | |
| I | 9 | 30 |
| II | 19 | 63 |
| III | 2 | 7 |
| Positive viral markers | | |
| Hepatitis B virus | 3 | 10 |
| Hepatitis C virus | 26 | 87 |
| Both | 1 | 3 |
| Child-Pugh classification | | |
| A | 20 | 67 |
| B | 10 | 33 |
| C | 0 | 0 |
| Pretreatment indocyanine green clearance at 15 minutes, % | | |
| < 15 | 0 | 0 |
| 15-40 | 21 | 70 |
| 40-50 | 5 | 17 |
| > 50 | 4 | 13 |
| Tumor size, mm | | |
| Median | 45 | |
| Range | 25-82 | |
| 20-50 | 19* | 63 |
| > 50 | 11 | 37 |
| Macroscopic vascular invasion | | |
| Yes | 12 | 40 |
| No | 18 | 60 |
| Morphology of primary tumor | | |
| Single nodular | 26 | 87 |
| Multinodular, aggregating | 1 | 3 |
| Diffuse | 2 | 7 |
| Portal vein tumor thrombosis | 1* | 3 |
| Serum alpha-fetoprotein level, ng/mL | | |
| < 300 | 21 | 70 |
| ≥ 300 | 9 | 30 |
| Histology | | |
| Well-differentiated | 10 | 33 |
| Moderately differentiated | 14† | 47 |
| Poorly differentiated | 2 | 7 |
| Differentiation not specified | 3 | 10 |
| Negative (radiologic diagnosis only) | 1 | 3 |
| Prior treatment | | |
| No | 13 | 43 |
| Recurrence | 6 | 20 |
| Local ablation/TACE | 11 | 37 |

Abbreviations: ECOG, Eastern Cooperative Oncology Group; TACE, transarterial chemoembolization.
*Includes one patient whose gross target volume was tumor thrombosis at the posterior branch of right portal vein as a result of postsurgical recurrence.
†Includes two patients with histological diagnoses that were defined in previous surgery.

listed in Table 1. All patients had underlying liver cirrhosis with an initial ICG R15 value of ≥ 15%. Thirteen patients received PRT as a first treatment for their HCC. Six patients had postsurgical recurrences, and 11 received unsuccessful local ablation and/or TACE to the targeted tumor before PRT. Histologic confirmation was not obtained in one patient who had tumor with typical radiographic features compatible with HCC. Vascular invasion was diagnosed as positive in 12 patients. Three patients had HCC of ≤ 3 cm in diameter; however, they were not considered as candidates for local ablation therapy because of tumor locations that were in close proximity to the great vessels or the lung.

### Adverse Events

All patients completed the treatment plan and received 76 $Gy_E$ in 20 fractions of PRT with a median duration of 35 days (range, 30 to 64 days). Prolongation of overall treatment time of more than 1 week occurred in four patients: three were due to availability of the proton beam, and one because of fever associated with grade 3 elevation of total bilirubin that spontaneously resolved within 1 week. Adverse events within 90 days from commencement of PRT are listed in Table 2. Decrease of blood cell count was observed most frequently. A total of 10 patients experienced transient grade 3 leukopenia and/or thrombocytopenia without infection or bleeding necessitating treatment. Of note, eight of them already had leuko- and/or thrombocytopenia, which could be ascribable to portal hypertension, before commencement of PRT corresponding to grade 2 in terms of the NCI-CTC criteria. Because none of the five patients experiencing grade 3 elevation of transaminases showed clinical manifestation of hepatic insufficiency and maintained good performance status, PRT was not discontinued. Nevertheless, these events spontaneously resolved within 1 to 2 weeks.

Development of hepatic insufficiency within 6 months after completion of PRT was defined as proton-inducing hepatic insufficiency (PHI), and this was observed in eight patients. Causal relationship between PHI and several factors are described separately below. One patient developed transient skin erosion at 4 months that spontaneously resolved within 2 months. Another patient developed painful subcutaneous fibrosis at 6 months that required nonsteroidal analgesics for approximately 12 months thereafter. Both of these skin changes developed at the area receiving ≥ 90% of the prescribed dose because the targeted tumors were located at the surface of the liver adjacent to the skin. However, they remained free from refractory ulcer, bleeding, or rib fracture.

**Table 2.** Adverse Events Within 90 Days From the Start of Proton Beam Radiotherapy

| Grade | 0 | 1 | 2 | 3 | 4 |
|---|---|---|---|---|---|
| Leukopenia | 7 | 2 | 13 | 8 | 0 |
| Thrombocytopenia | 2 | 6 | 15 | 7 | 0 |
| Total bilirubin | 20 | 2 | 7 | 1 | 0 |
| Transaminases | 4 | 8 | 13 | 5 | 0 |
| Nausea/anorexia | 23 | 7 | 0 | 0 | 0 |
| Overall (maximum grade) | 0 | 4 | 14 | 12 | 0 |

There were no observations made of gastrointestinal or pulmonary toxicity of grade 2 or greater in all patients. In addition, after percutaneous insertion of metallic markers, no serious adverse events, including bleeding or tumor seeding along the needle tracts, were observed.

### Tumor Control and Survival

At the time of analysis on November 2003, 12 patients had already died because of intrahepatic recurrence of HCC in seven, distant metastasis in two, and hepatic insufficiency without recurrence in three. Eleven of these 12 patients had been free from local progression until death; the durations ranged from 6 to 41 months (median, 8 months). One patient who had a single nodular tumor of 4.2 cm in diameter experienced local recurrence at 5 months and subsequently died of multifocal intrahepatic HCC recurrence. Otherwise, 18 patients were alive at 16 to 54 months (median, 31 months) without local progression. A total of 24 patients achieved complete disappearance of the primary tumor at 5 to 20 months (median, 8 months) post-PRT. Five had residual tumor mass on CT and MRI images for 3 to 35 months (median, 12 months) until the time of death (n = 4) or until last follow-up at 16 months (n = 1). As a whole, 29 of 30 enrolled patients were free from local progression until death or last follow-up, and the local progression-free rate at 2 years was 96% (95% CI, 88% to 100%). Tumor regression was associated with gradual atrophy of the surrounding noncancerous portion of the liver that initially suffered from radiation hepatitis,[20] as shown in Figure 1.

A total of 18 patients developed intrahepatic tumor recurrences that were outside of the PTV at 3 to 35 months (median, 18 months) post-PRT. Five of these occurred within the same segment of the primary tumor. Eight patients received TACE, and four received radiofrequency ablation for recurrent tumors; however, six did not receive any further treatment because of poor general condition in three and refusal in three. Five died without intrahepatic recurrence. Seven patients remained recurrence-free at 16 to 39 months (median, 35 months). Actuarial overall survival rates were 77% (95% CI, 61% to 92%), 66% (95% CI, 48% to 84%), and 62% (95% CI, 44% to 80%), and disease-free survival rates were 60% (95% CI, 42% to 78%), 38% (95% CI, 20% to 56%), and 16% (95% CI, 1% to 31%) at 1, 2, and 3 years, respectively (Fig 2).

### Correlation of Survival With Prognostic Factors

Overall survival was evaluated according to 10 factors as listed in Table 3. Univariate analyses revealed that factors

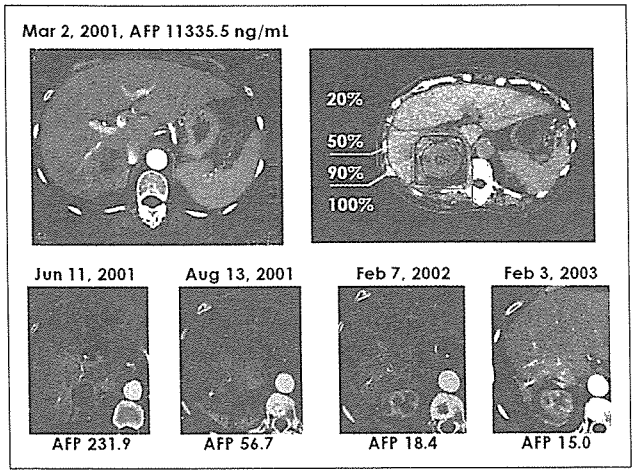


**Fig 1.** Case presentation: 70-year-old woman who received proton radiotherapy of 76 Gy in 20 fractions for 37 days from April 2, 2001, for her tumor located at the right posterior segment of the liver (left upper panel). Dose distribution was demonstrated in the right upper panel. Two portals from posterior and right lateral directions were used.

related to functional reserve of the liver and tumor size had significant influences on overall survival ($P < .05$). Liver function was the only independent and significant prognostic factor by multivariate analysis, as presented in Table 3. When clinical stage or Child-Pugh classification was substituted for ICG R15 as a covariate for liver function, the results of multivariate analyses were unchanged (data not shown). Overall survival according to pretreatment ICG R15 is shown in Figure 3.

### *Estimation of the Risk of Proton-Inducing Hepatic Insufficiency by Dose-Volume Histogram Analysis*

Eight patients developed PHI and presented with ascites and/or asterixis at 1 to 4 months after completion of PRT, without elevation of serum bilirubin and transaminases in the range of more than 3× the upper limit of normal. Of these, four died without evidence of intrahepatic tumor recurrence at 6 to 9 months; three died with recurrences of HCC at 4, 8, and 22 months; and one was alive at 41 months without tumor recurrence. DVH for hepatic noncancerous portions (entire liver volume minus gross tumor volume) was drawn according to pretreatment ICG R15 values (Fig 4A to C). The results showed that all of the nine patients with ICG R15 less than 20% were free from PHI and alive at 14 to 54 months. Three of the four patients with pretreatment ICG R15 $\geq$ 50% experienced fatal PHI without evidence of HCC recurrence, and another patient died of PHI with intrahepatic and systemic dissemination of HCC at 4 months. Among patients whose ICG R15 values ranged from 20% to 50%, all of the four patients whose percentage of hepatic noncancerous portions receiving $\geq$ 30 $Gy_E$ ($V_{30}$%) exceeded 25% developed PHI. On the other hand, none of the patients whose $V_{30}$% was less than 25% experienced PHI, as shown in Figure 4B ($P = .044$, Mann-Whitney $U$ test). Three-year overall survival for patients with either the $V_{30}$% $\geq$ 25% or ICG R15 $\geq$ 50% (n = 9) was 22% (95% CI, 0% to 50%), whereas it was 79% (95% CI, 60% to 98%) for the remaining 21 patients with favorable risk ($P = .001$).

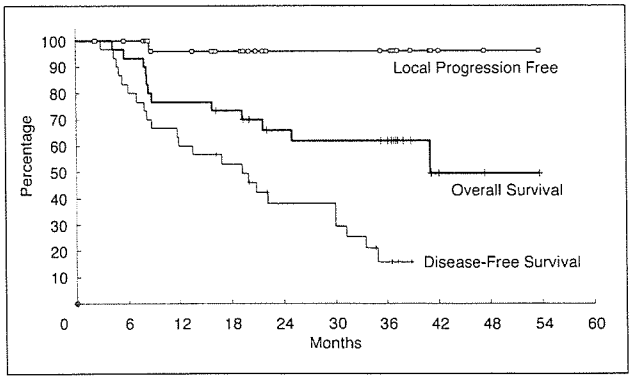


**Fig 2.** Kaplan-Meier estimate of local progression-free, overall, and disease-free survival rates for all 30 patients enrolled.

## DISCUSSION

The principal advantage of PRT lies in its possibility of aggressive dose escalation without prolongation of treatment duration in order to improve local control rate. The liver will be the most appropriate organ for this approach because it has a unique characteristic of developing compensatory hypertrophy when a part of this organ suffers from permanent damage. This study showed that the local control rate of PRT alone for patients with advanced HCC was consistent, as previously reported.[14] Slow regression of tumor volumes associated with gradual atrophy of surrounding noncancerous liver tissue was also in agreement with a previous report.[20] No serious gastrointestinal toxicity occurred, with careful patient selection performed in order to exclude these structures from PTV receiving high PRT dose. Eligibility criteria as to blood cell count in this study were eased up considerably in order to test the safety of PRT for patients with cirrhosis associated with portal hypertension. Nevertheless, no patients experienced serious sequelae relating to leukopenia or thrombocytopenia, which were the most frequently observed adverse events during PRT. All patients were able to complete their PRT basically in an outpatient clinic. Therefore we submit that the safety, accuracy, and efficacy of PRT administering 76 $Gy_E$/5 weeks using our newly installed Proton Therapy System and ReGIS for selected patients with advanced HCC has been confirmed.

Multivariate analysis suggested that the the functional reserve of the liver had significant influence on overall survival. Recent prospective series of untreated patients with

**Table 3.** Factors Related to Overall Survival

| Factor | No. of Patients | Overall Survival at 2 Years (%) | Univariate *P* | Multivariate *P* | Hazard Ratio | 95% CI |
|---|---|---|---|---|---|---|
| Age, years | | | .263 | .665 | 1.54 | 0.22 to 10.75 |
| < 70 | 15 | 59 | | | | |
| ≥ 70 | 15 | 71 | | | | |
| Sex | | | .829 | .732 | 1.44 | 0.18 to 11.65 |
| Male | 20 | 67 | | | | |
| Female | 10 | 60 | | | | |
| Tumor size, mm | | | .045 | .159 | 0.34 | 0.08 to 1.52 |
| 20 to 50 | 19 | 71 | | | | |
| > 50 | 11 | 44 | | | | |
| Pretreatment ICG R15 | | | .006 | .026 | 0.19 | 0.05 to 0.82 |
| ≤ 40% | 21 | 80 | | | | |
| > 40% | 9 | 30 | | | | |
| Clinical stage | | | < .001 | | | |
| I | 9 | 73 | | | | |
| II | 19 | 68 | | | | |
| III | 2 | 0 | | | | |
| Child-Pugh classification | | | .006 | | | |
| A | 20 | 78 | | | | |
| B | 10 | 38 | | | | |
| Vascular invasion | | | .930 | .650 | 1.44 | 0.30 to 7.03 |
| Yes | 12 | 67 | | | | |
| No | 18 | 66 | | | | |
| Serum AFP level, ng/mL | | | .313 | .061 | 0.20 | 0.04 to 1.07 |
| < 300 | 21 | 67 | | | | |
| ≥ 300 | 9 | 60 | | | | |
| $V_{30}$% | | | .213 | .141 | 0.25 | 0.04 to 1.58 |
| ≤ 25% | 24 | 65 | | | | |
| > 25% | 6 | 40 | | | | |
| Prior treatment | | | .455 | .091 | 3.63 | 0.82 to 16.18 |
| No | 13 | 69 | | | | |
| Recurrence | 17 | 60 | | | | |

Abbreviations: ICG R15, percentage of indocyanine green clearance at 15 minutes; AFP, alpha-fetoprotein; $V_{30}$%, percentage of hepatic noncancerous portion receiving ≥ 30 cobalt gray equivalent.

advanced HCC and underlying cirrhosis showed that overall survival rate at 3 years ranged from 13% to 38%, and rarely exceeded 50% even for those with most favorable prognostic factors.[1] In this study, actuarial overall survival rate at 3 years for all 30 patients including those who had HCC with vascular invasion and/or severe cirrhosis was 62%. Furthermore, 21 patients with initial ICG R15 of ≤ 50% and $V_{30}$% of ≤ 25% achieved 79% of overall survival rate at 3 years. All of the eight patients with favorable liver functional reserve (ICG R15, 15% to 20%) were alive at 20 to 54 months as shown in Figure 3. This suggests that adequate local control with PRT provides survival benefit for selected patients with HCC and moderate cirrhosis. On the other hand, prognoses of aggressive PRT were disappointing for patients, with poor functional liver reserve showing an ICG R15 of 50% or worse, and, therefore, indication of PRT for such patients was thought to be extremely limited.

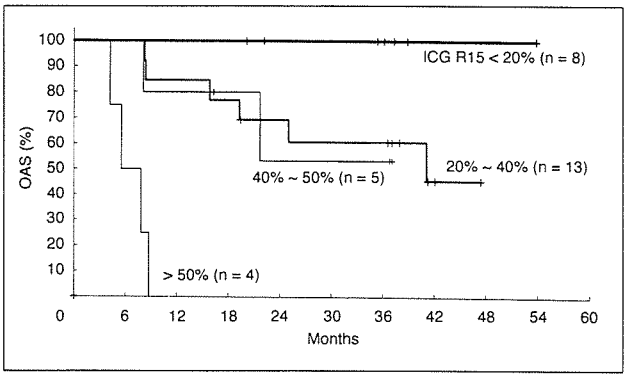


**Fig 3.** Overall survival (OAS) rates according to pretreatment indocyanine green clearance at 15 minutes (ICG R15).

A part of noncancerous liver suffering from PRT-inducing hepatitis gradually developed dense fibrosis and resulted in almost complete atrophy,[20] whereas the absorbed dose in a large proportion of the remaining liver was 0 $Gy_E$, as shown in Figures 1 and 4. This change is similar to

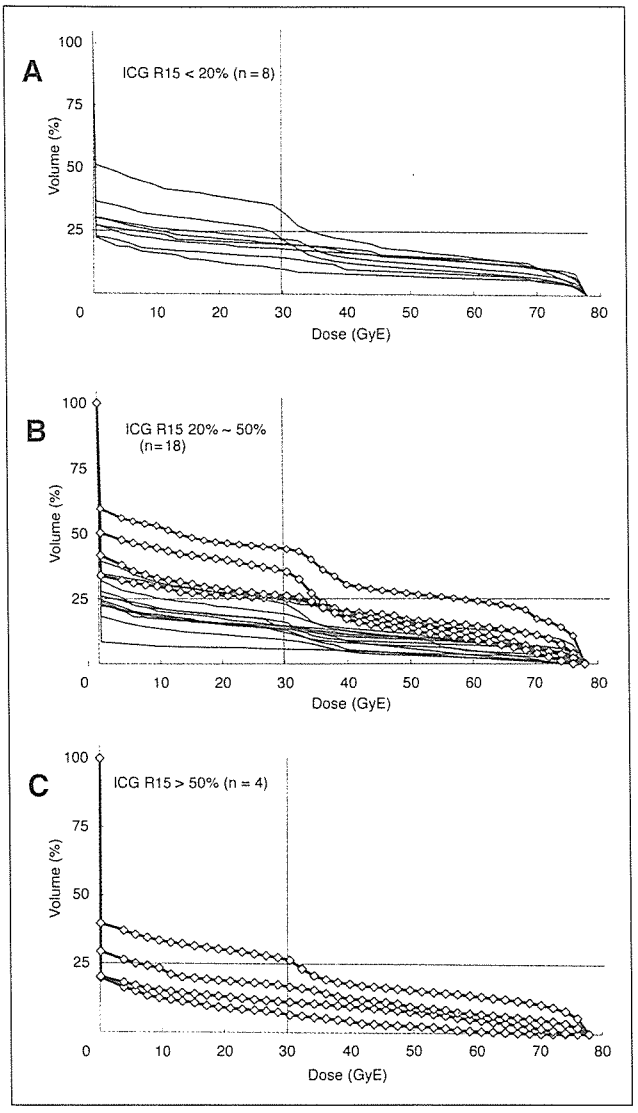


**Fig 4.** Dose-volume histogram (DVH) for all patients according to their pretreatment ICG R15 values, as noted in panels A, B, and C. Thick line with rhombi represents DVH for patients suffering from hepatic insufficiency within 6 months after completion of proton beam radiotherapy.

that seen in partial liver resection, rather than after 3-dimensional conformal or intensity-modulated radiotherapy delivering a low-dose of x-ray to a large proportion of noncancerous liver. Therefore, estimation of the risk of PRT-inducing hepatic insufficiency should be done with similar guidelines to evaluate liver tolerance to surgery, rather than that with normal tissue complication probability model using a mean dose administered to the entire liver.[21] Remnant liver volume and ICG R15 have been preferred indicators for that estimation, especially in Japan.[15] DVH analyses (Figs 4A to C) suggested that $V_{30}$% in combination with ICG R15 may be a useful indicator for estimation of liver tolerance to PRT, but no definite quantitative criteria emerged with the limited data obtained at present because of the small number of patients evaluated. The current staging system for HCC is based on survival data obtained in surgical series.[22] There is no reliable system to stratify the prognosis of patients with solitary but unresectable HCC on the assumption that they achieve good local control after PRT. Because of the limited availability of PRT at present, the establishment of particular criteria for patient selection using quantitative parameters of hepatic function such as ICG R15, and volume parameter like $V_{30}$%, is needed to maximize the cost-effectiveness of PRT.

Applicability of PRT instead of surgery for patients with early-stage disease should be considered with caution. Intraoperative ultrasonography (IOUS) has an important role in detecting small metastatic lesions, which could not be demonstrated in preoperative examinations. The high incidence of intrahepatic recurrences seen outside the PTV might be partly ascribable to the limit of pretreatment imaging studies. Infiltration of HCC to the portal vein and spread via portal blood flow is one of the mechanisms for the development of intrahepatic recurrence.[15] Actually, five recurrences occurred within the same segment of the primary tumor in this study. Although anatomic resection according to the architecture of the portal vein using IOUS offered a better chance of cure only for patients with noncirrhotic livers,[23] systematic segmental PRT based on multimodal imagings such as CT during arterial portography or MRI as well as image fusion technique[24] has a theoretical advantage compared with nonanatomic PRT confined to GTV only. Because there were few potentially curative approaches other than surgery for patients with HCC showing vascular invasion, further study is warranted to scrutinize an efficacy of PRT for patients with HCC of $\geq$ 5 cm in diameter, of which a large majority will demonstrate vascular invasion around the periphery of the tumor,[25] while giving attention to their $V_{30}$% values.

The risk of this aggressive dose-fractionation for sites such as the gastrointestinal loop, hepatic hilum, skin, or subcutanous tissues must be carefully considered, and more conventional fractionation must be adopted when these structures are critically involved in the PTV.

In conclusion, PRT for localized HCC using an aggressive dose-fractionation scheme (76 $Gy_E$ for 5 weeks) achieved excellent local control rate regardless of vascular invasion or tumor size, if $\leq$10 cm, without devastating acute toxicity. Further study is warranted to scrutinize adequate patient selection according to quantitative parameter of hepatic function, such as ICG R15, and irradiated noncancerous liver volume in order to maximize survival benefit of this promising modality.

### *Authors' Disclosures of Potential Conflicts of Interest*

The authors indicated no potential conflicts of interest.

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*Original article*

# Weekly paclitaxel as second-line chemotherapy for advanced or recurrent gastric cancer

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**Abstract**

***Background.*** **Paclitaxel scheduled every 3 weeks has shown a response rate of ~20% for gastric cancer, with modest hematological toxicity. Weekly administration of paclitaxel in patients with breast or ovarian cancer has shown equivalent efficacy and milder toxicity compared with an every-3 week schedule. We investigated, retrospectively, the antitumor effects and toxicity profiles of weekly paclitaxel for patients with metastatic or recurrent gastric cancer in clinical practice.**

***Methods.*** **In 38 patients who had metastatic or recurrent histologically confirmed gastric cancer and a history of one prior chemotherapy regimen, other than paclitaxel or docetaxel, paclitaxel (80 mg/m$^2$) was administered weekly, three times every 4 weeks, with short-term premedication.**

***Results.*** **All 38 patients had had prior chemotherapy that included 5-fluorouracil, the fluoropyrimidine anticancer drug S-1, or cisplatin. The median number of courses in the present regimen was 6 (range, 1–44+). Dose intensity was 55 mg/m$^2$ per week, corresponding to 92% of the planned dose (60 mg/m$^2$ per week). The overall response rate was 24% (6/25) in measurable lesions, and pleural effusion and ascites disappeared in 2 of 7 patients (29%) and in 3 of 21 patients (14%), respectively. Median survival time was 151 days from the commencement of this treatment, with a median follow-up period of 260 days. Grade 3 or 4 leukopenia and neutropenia were observed in 11 (29%) and 12 (32%) patients, respectively. Seven patients (18%) died within 30 days of the last administration of paclitaxel.**

***Conclusion.*** **Weekly paclitaxel seems to be active as second-line chemotherapy against metastatic and recurrent gastric cancer. Further study is needed to confirm the efficacy and safety of weekly paclitaxel.**

**Key words** Gastric cancer · Weekly paclitaxel · Second-line chemotherapy

*Offprint requests to:* S. Hironaka

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## Introduction

Gastric cancer remains as one of the major causes of death from cancer worldwide. Despite a markedly improved survival trend through early detection and curative surgery, approximately 50000 deaths from gastric cancer occurred in Japan in 1997 [1]. Although patients with metastatic and recurrent gastric cancer still have a poor prognosis, no standard chemotherapy regimen has been established, even as the first-line.

Paclitaxel is an antitumor agent active against various kinds of malignancies. Because paclitaxel is known to be a cell-cycle-specific agent [2,3], basic research has suggested that prolongation of exposure might enhance its cytotoxic effects. In a phase I study of weekly paclitaxel, a regimen of 80 mg/m$^2$ in a 3-weeks-on and 1-week-off schedule was recommended [4]. In this phase I study, a weekly paclitaxel regimen (1-h infusion) produced objective tumor regression in patients previously treated with paclitaxel on a once-every-3-weeks schedule. Recently, successful results have been achieved using a regimen of weekly paclitaxel in patients with breast cancer and ovarian cancer. Hematological toxicity caused by a weekly 3-h infusion schedule has been reported to be milder, with equivalent activity, compared with a schedule of one 24-h infusion every 3 weeks [5].

Paclitaxel is recognized as one of the active cytotoxic agents for gastric cancer [6–9]. A weekly paclitaxel regimen has become popular in Japan, mainly as second-line chemotherapy, because of its milder hematological toxicity compared with a once every 3 weeks schedule of paclitaxel. However, only a few trials of weekly paclitaxel in patients with gastric cancer have been reported [10,11]. In the present retrospective study, we investigated the potential and safety of this more dose-dense weekly paclitaxel regimen in patients with pretreated gastric cancer.

## Patients and methods

### *Patients*

The subjects of this study consisted of 38 patients with metastatic or recurrent gastric cancer treated weekly with paclitaxel between September 2002 and September 2004 at the Shizuoka Cancer Center, Shizuoka, Japan. The recruitment criteria were as follows: (1) histologically proven adenocarcinoma of the stomach; (2) history of one prior chemotherapy regimen not involving paclitaxel or docetaxel; (3) age, 75 years or less; (4) performance status of 2 or less on the Eastern Cooperative Oncology Group scale; (5) adequate bone marrow, hepatic, and renal functions; (6) no other serious disease; (7) and oral or written informed consent given before the commencement of treatment.

### *Treatment methods*

The treatment schedule comprised an intravenous infusion of paclitaxel at 80 mg/m$^2$ in 250 ml normal saline over 1 h, repeated weekly three times for 4 weeks. Short-term premedication for paclitaxel-associated hypersensitivity reactions was used: dexamethasone, 8 mg; diphenhydramine, 50 mg; ranitidine, 50 mg; and granisetron, 3 mg were administered 30 min before the paclitaxel treatment. This treatment was repeated until disease progression or prohibitive toxicity, usually on an outpatient basis. In the event of serious hematological toxicity, treatment was suspended until recovery. If grade 4 hematological or grade 3 or 4 nonhematological toxicity occurred, the dose of paclitaxel was reduced to 60 mg/m$^2$.

### *Response and toxicity assessments*

Tumor measurements for response assessment in patients with primary lesions were made every 1 to 2 months by computed tomography (CT) and endoscopy. Objective responses in measurable metastatic lesions were evaluated according to the response evaluation criteria for solid tumors [12]. Survival time was calculated from the date of the commencement of paclitaxel treatment to the date of death or the last confirmation of survival. Symptomatic toxicity and laboratory data were monitored every week at the outpatient clinic. Toxicity was evaluated according to the National Cancer Institute common toxicity criteria (version 2).

## Results

### *Patient population*

Of 51 patients with advanced or recurrent gastric cancer treated with weekly paclitaxel as second-line chemotherapy, 38 patients fulfilled the recruitment criteria, and were included in this study. The 13 excluded patients had severe medical complications: 4 patients were aged 76 years or more, and 9 were performance status 3 or more.

Patient characteristics are presented in Table 1. Most (63%) were male, and the median age was 63 years. Twenty seven (71%) had a performance status of 0 or 1. All patients had had prior fluorouracil-based chemotherapy as first-line chemotherapy. Seven patients had pleural effusion and 21 had ascites. The number of metastatic organs (including liver, lymph node [LN], peritoneum, lung and bone), was one organ in 15 patients, two organs in 14 patients, and three organs or more in 9 patients.

### *Dose intensity*

The total number of administrations of paclitaxel was 364. The median number of courses per patient was 6 (range, 1–44+). Dose intensity was calculated as 55 mg/m$^2$ per week, which corresponded to 92% of the planned dose. This treatment was stopped in 35 patients, because of disease progression in 31 patients,

**Table 1.** Patient characteristics

| | |
|---|---|
| No. of patients | 38 |
| Sex | |
| Male | 24 |
| Female | 14 |
| Age (years) | |
| Median | 63 |
| Range | 51–73 |
| Performance status | |
| 0 | 12 |
| 1 | 15 |
| 2 | 11 |
| Prior chemotherapy | |
| S-1 | 29 |
| MTX + 5-FU | 4 |
| S-1 + CDDP | 2 |
| 5-FU | 1 |
| 5-FU + CDDP | 1 |
| UFT | 1 |
| Histology | |
| Intestinal | 13 |
| Diffuse | 21 |
| Unknown | 4 |
| Sites of metastasis[a] | |
| Liver | 10 |
| Lymph node | 21 |
| Peritoneum | 29 |
| Lung | 2 |
| Bone | 4 |
| Pleural effusion | 7 |
| Ascites | 21 |

[a] Some patients had metastases at multiple sites

**Table 2.** Toxicity

| | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Percentage ≥ grade 3 |
|---|---|---|---|---|---|
| Leukocytes | 7 | 5 | 9 | 2 | 29 |
| Neutrophils | 4 | 6 | 6 | 6 | 32 |
| Platelets | 2 | 2 | 3 | 0 | 8 |
| Nausea | 6 | 2 | 1 | — | 3 |
| Vomiting | 4 | 0 | 0 | 0 | 0 |
| Anorexia | 7 | 8 | 1 | 0 | 3 |
| Diarrhea | 4 | 1 | 1 | 0 | 3 |
| Neuropathy—motor | 0 | 0 | 1 | 0 | 3 |
| Neuropathy—sensory | 0 | 9 | 1 | 0 | 3 |
| Edema | 3 | 1 | 1 | 0 | 3 |
| Allergic reactions | 3 | 0 | 0 | 0 | 0 |

infection in 1, neuropathy in 1, refusal of further treatment in 1, and non-cancer death related in 1 patient.

*Toxicity*

Toxicity data are presented in Table 2. Of hematological toxicities, 11 patients (29%) experienced leukopenia of grade 3 or 4 and 12 (32%) had neutropenia of grade 3 or 4. Of nonhematological toxicities, 1 patient (3%) had grade 3 nausea and anorexia. Severe neuropathy was seen in 1 patient (3%) and no allergic reaction was seen in any patient. Seven patients (18%) died within 30 days of the last administration of paclitaxel. The reasons for these early deaths were disease progression in 3 patients; death of other causes (acute myocardial infarction in 1 and heart failure in 1); perforation of the esophagus in 1 (due to an inserted expandable metallic stent for esophageal stenosis caused by mediastinal lymph-node metastasis); and sepsis with grade 4 neutropenia in 1.

*Responses and survival*

Twenty-five of the 38 patients were assessable for response (13 patients did not have measurable disease). Of these 25 patients, 6 (24%) experienced a partial response (Table 3). The details of the responders are shown in Table 4. Pleural effusion disappeared in 2 of 7 patients (29%) and decreased in 1 of 7 patients (14%) after treatment with paclitaxel. Ascites disappeared in 3 of 21 patients (14%) and decreased in 2 of 21 patients (10%). The median follow-up period was 260 days. Survival data were updated in February 2005. The median survival time was 151 days after the initiation of weekly paclitaxel therapy (Fig. 1). The median time to progression was 64 days (Fig. 2). Twenty-one patients (55%) had no further chemotherapy after disease progression following paclitaxel therapy. Nine patients had irinotecan-containing regimens, 2 had a 5-fluorouracil (5-FU)-based regimen, 1 had intraperitoneal administration of cisplatin (CDDP), and 1 had palliative radiation therapy at the primary site.

**Table 3.** Response

| *n* | PR | SD | PD | NE | RR |
|---|---|---|---|---|---|
| 25 | 6 | 4 | 14 | 1 | 24% |

PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable; RR, response rate

## Discussion

Recently, weekly paclitaxel has been commonly used in second-line or higher chemotherapy. In the present retrospective study, all 38 patients had a history of prior chemotherapy at our institution. Moreover, 9 patients (24%) had three involved metastatic sites, and 4 (11%) had bone metastases. Seven patients had pleural effusion and 21 had ascites. To clarify the activity and toxicity of paclitaxel as second-line chemotherapy in a clinical practice setting, the recruitment criteria for this study allowed patients to have pleural effusion and/or ascites.

We found weekly paclitaxel therapy to be well tolerated by most patients, considering the dose intensity used and its toxicity profile. Previous reports showed that grade 3 or 4 neutropenia occurred in 37%, and grade 4 neutropenia in 67% of patients treated with paclitaxel on an every-3-weeks regimen [7,9]. In our study, 29% and 32% of patients had severe leukopenia and severe neutropenia, respectively. On the basis of these results, a weekly regimen of paclitaxel seems to be less toxic than an every-3-weeks regimen in terms of